A nomogram by adding atrial fibrillation to multicenter stroke survey score to predict intracranial hemorrhage in stroke patients undergoing thrombolysis

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Research article

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Abstract

Background: Identification of stroke patients at risk of postthrombolysis intracranial hemorrhage (ICH) in the clinical setting is essential. However, studies in this area spare.We aimed to develop a nomogram by adding atrial fibrillation to the Multicenter Stroke Survey (MSS) score to predict the probability of ICH in acute ischemic stroke patients undergoing thrombolysis. Methods: A retrospective observational study was conducted with 287 participants from a single center (67.2% males, median age 65 years). Head computed tomography scan was performed after 24 hour to evaluate ICH occurrence, and a computed tomography scan was done immediately in case of clinical worsening. The risk factors associated with ICH were analysed. Based on multivariate logistic model, a nomogram was generated for ICH on the basis of atrial fibrillation and the MSS score. We assessed the discriminative performance by using the area under curve (AUC) of receiver-operating characteristic (ROC) and calibration of risk prediction model by using calibration plot. Results: A total of 41(14.3%) ICH events occurred.The MSS score and atrial fibrillation were independent predictors of ICH in multivariate logistic regression analysis. Discrimination of the nomogram was superior to the MSS score alone (0.794 vs 0.741; P=0.034). The model was internally validated by using bootstrap (1000 samples) with AUC-ROC of 0.795. The calibration plot showed good agreement. Conclusion: We developed and internally validated a new nomogram using the MSS score and atrial fibrillation as predictors.The nomogram is a simple and accurate tool for predicting ICH in acute ischemic stroke patients undergoing thrombolysis. Further studies are warranted to validate our findings.

Background

Stroke is a leading cause of death and disability worldwide. Intravenous recombinant tissue plasminogen activator (r-tPA) treatment is an effective therapy for acute ischemic stroke [1]. However, intracerebral hemorrhage (ICH), especially symptomatic ICH (sICH), is the main complication of thrombolytic therapy and may increase the risk of poor and fatal outcomes [2]. The ICH occurrence rate after thrombolysis varies by ethnicity, and the rate of ICH is reported to be 2.12-fold higher in Asian populations than in non-Asian populations [3,4].

Accurate identification of stroke patients at increased risk of future postthrombolysis ICH in the clinical setting is essential. Several prognostic scores have been applied to identify stroke patients with a high risk of postthrombolysis ICH [5,6]. The Multicenter Stroke Survey (MSS) score has been shown to be a useful tool to predict sICH in Chinese population [5]. The MSS score is based on four variables (age, platelet count, glucose level and National Institute of Health Stroke Scale (NIHSS) score on admission) that are available before thrombolysis treatment [7]. In addition, the MSS score does not require imaging, making it particularly suitable for nonneurologists. However, the predictive value of the MSS score varied and was poor in some studies [5,6,8], which might be due to some potential risk factors not fully captured by the scoring system when used in different populations. Growing evidence supports that atrial fibrillation (AF) is an independent risk factor for ICH events and is associated with poor outcomes in acute ischemic stroke patients undergoing thrombolysis [9,10]. However, few score systems for ICH after thrombolysis had considered AF as a predictor.

Nomogram is a useful and better visual tool to predict clinical outcomes than the conventional scoring systems. It is a graphical statistical instrument that incorporates some variables to develop a scoring system, which reflects the individual and precise risk probability. However, the prognostic nomogram for ICH events in stroke patients undergoing thrombolysis is currently lacking [11,12].

The aim of the present study was to develop a nomogram by adding AF to the MSS score to predict the probability of ICH in acute ischemic stroke patients undergoing thrombolysis.

Methods

Study Population and Design

A retrospective cohort study was conducted at The First Affiliated Hospital of Xi'an Jiaotong University between April 2014 and Dec 2018. All of the patients had a clinical diagnosis of acute ischemic stroke according to the World Health Organization (WHO) criteria and were further confirmed by head computed tomography (CT) or magnetic resonance imaging (MRI). Among 340 eligible patients, we excluded 10 patients who had missing data at admission (2.9%) and 43 patients who underwent intra-arterial thrombolysis or intravenous r-tPA treatments combined with mechanical thrombectomy (12.6%). After exclusion, 287 patients were included in the final analysis in the present study (Fig 1). Patient data were extracted from their medical charts. This retrospective study was reviewed and approved by the Institutional Review Board of Xi'an Jiaotong University. The need for patient consent was waived by the same ethics committee.

Baseline Data Collection

The baseline demographic, clinical and laboratory information collected included age, sex; current smoking status, glucose level on admission, triglyceride (TG) level, low-density lipoprotein cholesterol level (LDL-C), platelet count; antiplatelet therapy before enrollment, systolic and diastolic blood pressures, NIHSS score on admission, symptom onset to treatment (ONT), and histories of hypertension, diabetes mellitus and AF.

Calculation of the MSS Score

The MSS score has been previously described [7]. The score was derived from four variables (age > 60 year, platelet count ≥ 150,000/mm^3, glucose level >8.325 mmol/L and NIHSS score > 10 on admission) and calculated for each patient. All baseline MSS scores at discharge were calculated by a stroke neurologist.

Thrombolysis Method

All patients were treated with r-tPA within 4.5 hours of onset. Intravenous r-tPA (alteplase, 0.9 mg/kg up to a maximum of 90 mg) was used with 10% of the total dose as a bolus, followed by a 60-min infusion of the remaining dose.

Ascertainment of Intracranial Hemorrhage

On admission, all patients underwent a CT scan within the first 4.5 hours of stroke onset. CT was repeated 24 hours after intravenous r-tPA, and another CT scan was performed immediately in cases of rapid neurological deterioration to evaluate the presence of ICH. SICH was defined as any type of ICH on any posttreatment imaging after the initiation of thrombolysis and an increase in NIHSS by 4 points from baseline or death; asymptomatic ICH (aSICH) was defined as any type of ICH on any posttreatment imaging after thrombolysis start but not accompanied by neurological deterioration (the European Cooperative Acute Stroke Study II, ECASS II) [13].

Statistical Analysis

Descriptive analysis was conducted with continuous variables described as medians with interquartile ranges (IQRs) or as the means with standard deviations (SDs) if the variables had normal distributions. Categorical variables are presented as numbers (percentages). Baseline demographic and clinical characteristics were compared by Student’s t-test for continuous variables and the chi-square test for categorical variables. The associations between risk factors and ICH were estimated by odds ratios (ORs) and 95% confidence intervals (CIs) using multivariate logistic regression models. Variables ($P \le 0.1$) in the univariate analysis were included in the multivariate model.

Nomogram was generated by inputing the predictors of AF and the MSS score into the multivariate logistic regression model to generate a scoring system.The predictive accuracy of the nomogram model was assessed by calculation of the area under the receiver operating characteristic curve (AUC-ROC). Calibration was carried out using calibration plot, in which the predicted probabilities were plotted against the frequency of the observed outcome. The prediction of a well-calibrated model should be morrored by a 45º diagonal line. The coefficient of determination of R^2 was calculated. Given that all predictive equations tend to be over-fitted to the original sample, the model was internally validated using the bootstrapping methods with 1000 re-samples.

The statistical analysis was performed using SPSS version 22.0 (SPSSInc, Chicago, IL, USA) and the statistical software package R version 3.5.3. DeLong’s test was used to compare the AUC of each of the models, which were analyzed by use of MedCalc Version 18.2.1. Two-tailed significance values were applied, and statistical significance was defined as $P<0.05$.

Results

Baseline Characteristics of Patients

During 2004-2018, there were 340 patients treated with intravenous thrombolysis in our center. After exclusion (n=53, 15.6%), 287 remaining patients were eligible for analysis (Fig 1). The baseline characteristics of patients with and without ICH are shown in Table 1. The median age was 65 years (range, 27-93), and 67.2% were men. A total of 41(14.3%) ICH events occurred in stroke patients after thrombolysis. The variables associated with ICH in the univariate analysis were older age (P=0.025), baseline NIHSS (P<0.001), initial glucose level (P=0.001), AF (P<0.001), platelet count (P=0.076), antiplatelet therapy (P=0.017) and the MSS score (P<0.001). The median MSS score was 1 for total patients and 2 for ICH patients.

The MSS score could range from 0 to 4 with an increasing score corresponding to an increase in postthrombolysis ICH incidence (online supplement Fig 1). The ICH incidence for the MSS score of 0, 1, 2, 3 and 4 was 3.9%, 4.8%, 22.1%, 30% and 50%, respectively.

Risk score and nomogram development

A` nomogram based on AF and the MSS score was developed from the results of multivariate logistic regression by assigning a weighted score to each of the two independent prognostic factors. The discriminative performance of the nomogram (evaluated by means of AUC-ROC) was 0.794 (95% CI 0.745-0.840) in the present study. The AUC increased from 0.741 for the MSS score alone to 0.794 for the MSS score combined with AF (difference in the AUCs, 0.053, z value 2.12, P=0.034) (Fig 2). The model was internally validated by using bootstrap (1,000 samples) to calculate the discrimination with accuracy, and the good predictive performance of the nomogram was confirmed with AUC of 0.795 (95% CI 0.717-0.871; P<0.001). The calibration of the nomogram presented a good agreement between predicted risk and observed incidence rates of ICH after thrombolysis (R^2=0.238, P 0.05) (Fig 3)

Discussion

The present study demonstrated that adding AF to the MSS score increased the predictive value of the MSS score for ICH. We developed and internally validated a nomogram based on AF and the MSS score to predict the probability of ICH in stroke patients treated with alteplase. The new nomogram showed a significantly higher predictive accuracy than the conventional scoring system of the MSS score.

Among the computational models for predicting prognosis, the nomogram is very useful because it is a pictorial representation of a statistical predictive model that generates a numerical probability of a clinical event. It is more accurate than the conventional method using OR [14]. Therefore, we constructed a nomogram that can calculate the probability of ICH for an individual stroke patients undergoing thrombolysis. The parameters constructed in our model are easily available in almost all medical centers and all patients within few minutes of their arrival to the emergency room.

To the best of our knowledge, there have only 2 works carried out on nomograms for individualized prediction of the ICH probability in acute ischemic stroke patients undergoing thrombolysis [11,12]. The STARTING-SICH nomogram including 10 variables was designed to predict sICH in stroke patients treated with intravenous thrombolysis in a large cohort study of Italy [11], but it has not been external validated in Asian patients and the data on ethnicity are lacking. The other nomogram model including 3 variables (present of AF, NIHSS score and glucose level on admission) was developed in Asian patients [12]. However, the study did not include the information about the total dose of r-PA, and the risk of ICH is reported higher in Asian populations at standard doses [15].

Our nomogram used only two prognostic factors including AF and an existing scoring system (the MSS score). The MSS score is widely used. History of AF is easily and readily obtainable during the patient's admission at the hospital. Our nomogram was the first approach to combine AF and the MSS score to predict ICH in stroke patients. This combination approach had more accurate predictive power than the MSS score alone. Researchers recently compared different ICH risk scores and found that ORs based on logistic models and AUC-ROC values for the MSS scores showed improved performance, with values ranging from 0.63 to 0.86 [5,6,8]. The present study demonstrated that the AUC-ROC value for the MSS score was 0.741 for ICH, and the predictive value increased significantly to 0.794 when the MSS score was combined with AF. This easy-to-use simultaneous testing model that adding AF to the MSS score, with noninvasive clinical characteristics, can provide an immediate and reliable estimation of ICH risk in acute ischemic stroke patients who require thrombolysis. This estimate will guide clinicians not only in counseling patients and/or families but also in the early identification of those patients at high risk of ICH as well as support decisions regarding additional treatments or more attention.

Early ischemic signs on CT or even hyperdense cerebral artery signs are difficult to interpret and require experienced personnel or experts to evaluate, as reported by Thanin et al [16]. Therefore, some scoring systems, including the MSS score [7], Safe Implementation of Thrombolysis in Stroke (SITS)-SICH score [17], Glucose Race Age Sex Pressure Stroke Severity (GRASPS) score [4] and Stroke Prognostication using Age and National Institutes of Health (NIH) Stroke Scale (SPAN-100) positive index [18], have no CT component in their scoring systems. Most scoring systems are derived from Western countries that might have different sets of prognostic parameters. The MSS score was derived from a North American and European study within a 3-hour time window, whereas the present study with a Chinese study employed a 4.5-hour time window. A previous study reported that the MSS score could predict sICH (ECASSII definition) with an AUC of 0.730 in Chinese stroke patients [5]. The AUC for the MSS score alone was 0.741 for ICH in the present study; therefore, we speculated that this result might be due to some potential risk factors not fully captured by the scoring system when external validated in Chinese population.

Studies have reported additional predictive factors for postthrombolysis ICH, including leukoaraiosis, high mean blood pressure, low serum albumin and the neutrophil to lymphocyte ratio [19-22]. However, these identified risk factors accounted for only a proportion of the stroke patients who presented ICH after intravenous thrombolysis. Growing evidence supports that AF is an independent risk factor for ICH events [9,10,23]. However, AF has not been considered in previous risk scoring systems for ICH after thrombolysis [4,7,17,18,24,25]. Yeo et al reported a scoring system using nomogram based on three variables (presence of AF, glucose level and NIHSS score) was a practical tool to predict the risk of ICH after thrombolysis [12]. In our study, the AF prevalence at baseline was higher in patients with ICH and was an independent risk factor for ICH in stroke patients undergoing thrombolysis. Furthermore, we found that AF and the MSS score were correlated, and the patients with AF had higher MSS score. Moreover, adding AF to the MSS score on admission enhanced the predictive value of ICH for stroke patients with thrombolysis.

We included both symptomatic and asymptomatic postthrombolysis ICH as the outcome for the scoring systems, as in previous studies [7,12]. Many reports have demonstrated that both symptomatic and asymptomatic ICH may worsen clinical outcomes [7,26,27], and influence the timing of reintroducing antithrombotic treatment after r-tPA treatment. Furthermore, predicting a higher risk of ICH preceding intravenous thrombolysis may help clinical decision making by slanting treatment toward only mechanical thrombectomy without intravenous r-tPA [12].

There are some limitations of the study. First, the present study used a retrospective design, so some confounders were not available for inclusion in our multivariate analyses. Second, the study included a single center based sample and a relatively small sample size, which might have limited the statistical power of the results. Finally, although we internally validated our model using bootstrap resampling, our model has not been validated in external cohorts.

Conclusions

AF in stroke patients undergoing thrombolysis was positively related to the ICH and improved the predictive value of the MSS score for ICH. We developed and internally validated a nomogram based on the MSS score and AF to predict the risk for ICH. The nomogram is simple and easy to use and has improved predictive performance for ICH in acute ischemic stroke patients prior to thrombolysis in Chinese population. Further studies are warranted to validate our findings.

Abbreviations

ICH: Intracranial hemorrhage; MSS score: Multicenter Stroke Survey score; AUC: Area under curve; ROC: Receiver-operating characteristic; r-tPA: Recombinant tissue plasminogen activator; NIHSS: National Institute of Health Stroke Scale; CT: Computed tomography; MRI: Magnetic resonance imaging; sICH: Symptomatic intracranial hemorrhage; aSICH: Asymptomatic intracranial hemorrhage; AF: Atrial fibrillation; ECASS II: European Cooperative Acute Stroke Study II; WHO: World Health Organization; IQR: Interquartile range; SD: Standard deviation; OR: Odds ratio; CI: Confidence interval; The SITS SICH: The Safe Implementation of Treatments in Stroke symptomatic intracerebral hemorrhage; SITS-MOST: Safe implementation of thrombolysis in stroke-monitoring study; FPG: Fasting plasma glucose; TG: Triglyceride; LDL-C: Low-density lipoprotein cholesterol level; ONT: Symptom onset to treatment; GRASPS: Glucose Race Age Sex Pressure Stroke Severity; SPAN-100: Stroke Prognostication using Age and National Institutes of Health (NIH) Stroke.

Declarations

Acknowledgments

Not applicable.

Authors' contributions

Changqing Miao and Xiaoyan performed sample collection, participated in its design, acquired data, interpreted the results, performed statistical analyses and drafted the manuscript. Yin Simin Liang and Chunying Mu participated in sample collection, acquired data and helped in the interpretation of results. Yurong Zhang designed the study, interpreted the results, performed statistical analyses, revised the manuscript and approved the version of the manuscript to be published. All authors read and approved the final manuscript.

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Availability of data and materials

Data used for this study cannot be made publicly available because additional studies are currently under way using the same data set, but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This retrospective study was reviewed and approved by the Institutional Review Board of Xi'an Jiaotong University. The need for patient consent was waived by the same ethics committee.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Characteristics of the study participants.

Characteristic	Total (n=287)	ICH (n=41)	without ICH (n=246)	P value
Demographic data				
Age (year) (median, IQR)	65 (56-73)	70 (62-75)	64 (55-73)	0.025
Male, n (%)	193 (67.2)	24 (58.5)	169 (68.7)	0.199
Current smoking, n (%)	123 (42.9)	17 (41.5)	106 (43.7)	0.341
Medical history, n (%)				
Diabetes mellitus	77 (26.8)	15 (36.6)	62 (25.2)	0.128
Atrial fibrillation	74 (25.8)	23 (56.1)	51 (20.7)	<0.001
Hypertension	190 (66.2)	30 (73.2)	160 (65.0)	0.308
Laboratory tests				
Glucose (mg/dL) (median, IQR)	7.5 (6.5-8.5)	8.6 (7.2-9.8)	7.3 (6.4-8.3)	0.001
TG (mmol/L) (median, IQR)	1.3 (0.9-1.8)	1.5 (1.0-1.9)	1.3 (0.9-1.8)	0.190
LDL-C (mmol/L) (mean±SD)	2.5 ± 0.8	2.5 ± 0.9	2.4 ± 0.8	0.538
PLT count (10^9/L) (median, IQR)	181 (148-220)	172 (134-206)	182 (151-224)	0.076
Parameters on admission				
Systolic BP (mmHg) (median, IQR)	150 (134-167)	151 (139-173)	150 (134-165)	0.575
Diastolic BP (mmHg) (median, IQR)	84 (74-99)	82 (70-101)	84 (75-98)	0.466
NIHSS score (median, IQR)	6.0 (3.0-12)	12 (7.0-16)	5.0 (3.0-10)	<0.001
ONT (hour) (median, IQR)	3.0 (2.3-4.0)	3.0 (2.0-3.6)	3.0 (2.5-4.0)	0.080
Antiplatelet therapy, n (%)	63 (22.0)	15 (36.6)	48 (19.5)	0.017
MSS score (median, IQR)	1.0 (1.0-2.0)	2.0 (2.0-3.0)	1.0 (1.0-2.0)	<0.001

Notes: Continuous variables are expressed as the median (IQR) or as the mean with SD; categorical variables are expressed as frequency (percent).

Abbreviations: ICH, intracranial hemorrhage; IQR, interquartile range; SD, standard deviation; NIHSS, National Institutes of Health Stroke Scale; ONT, symptom onset to treatment; PLT count, platelet count; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; BP, blood pressure; MSS, multicenter stroke survey.

Table 2 Associations of the MSS score and atrial fibrillation with ICH.

Variables	Univariate analysis OR (95% CI)	P value	Multivariate analysis* OR (95% CI)	P value*
MSS score	2.61 (1.80-3.78)	<0.001	2.37 (1.60-3.52)	<0.001
Atrial fibrillation	4.89 (2.45-9.74)	<0.001	3.92 (1.83-8.41)	<0.001

Abbreviations: OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; MSS, multicenter stroke survey.

*Adjusted for: symptom onset to treatment and antiplatelet therapy.

Figures

Fig 1.

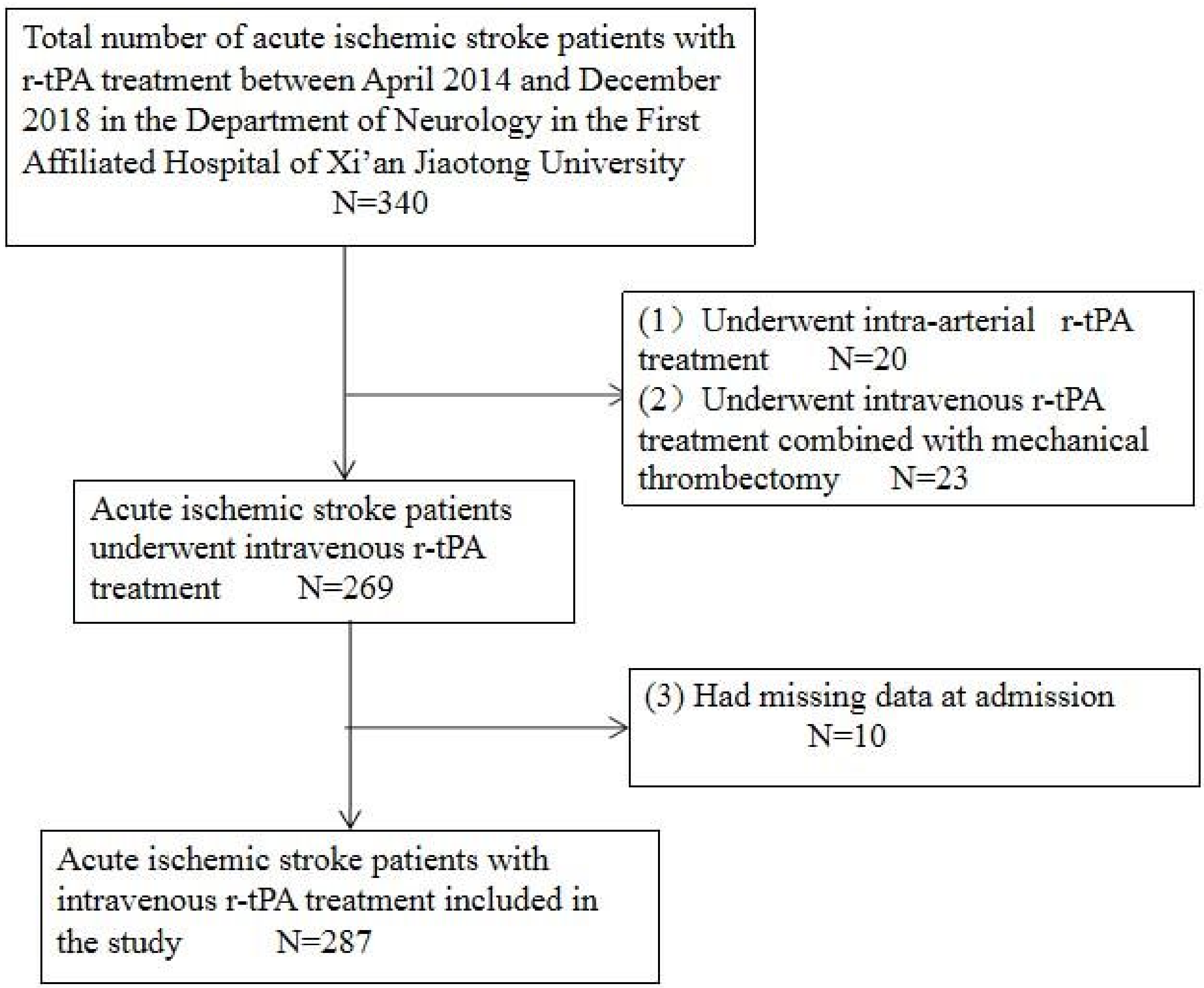

Figure 1

Three hundred forty cases of acute ischemic stroke patients receiving intravenous r-tPA treatment and reasons for exclusion

Fig. 2

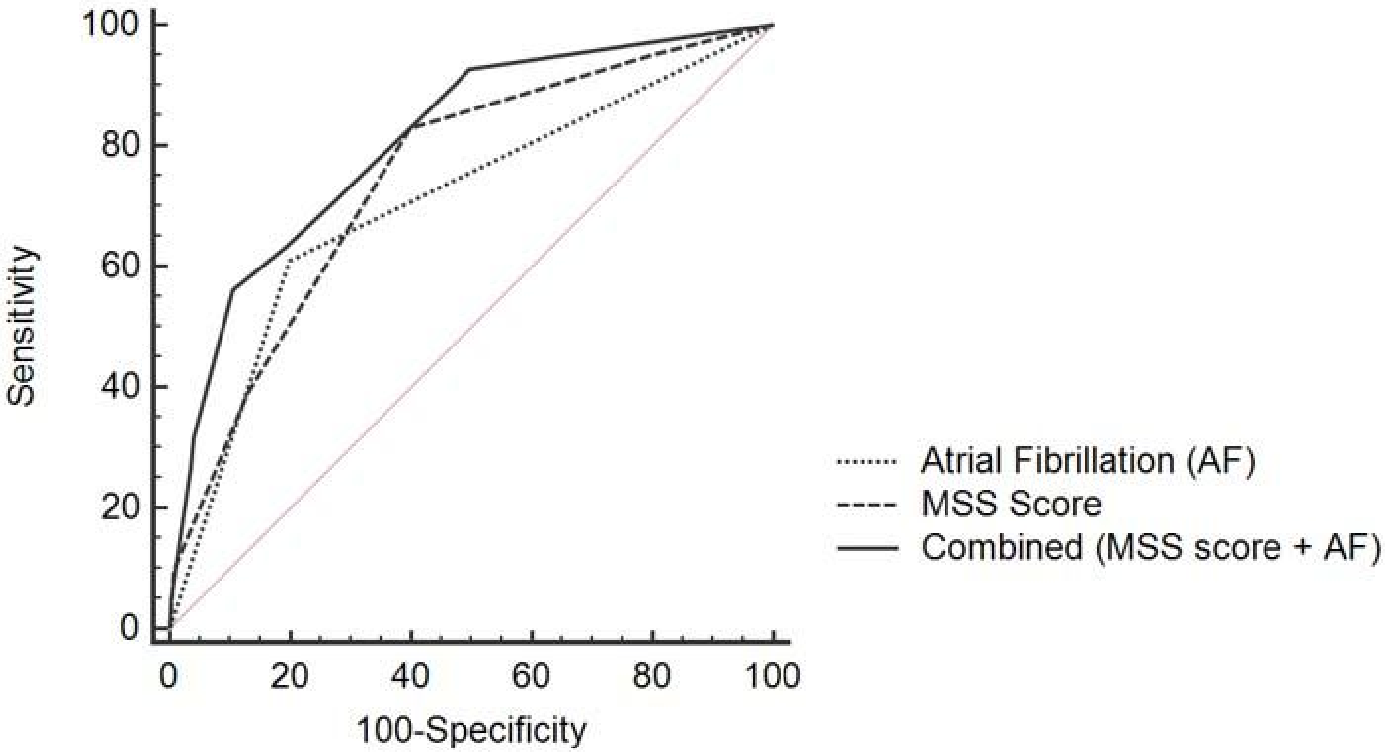

Figure 2

Receiver operating characteristic (ROC) curve of different models to predict intracerebral hemorrhage (ICH) atfer thrombolysis

Fig. 3

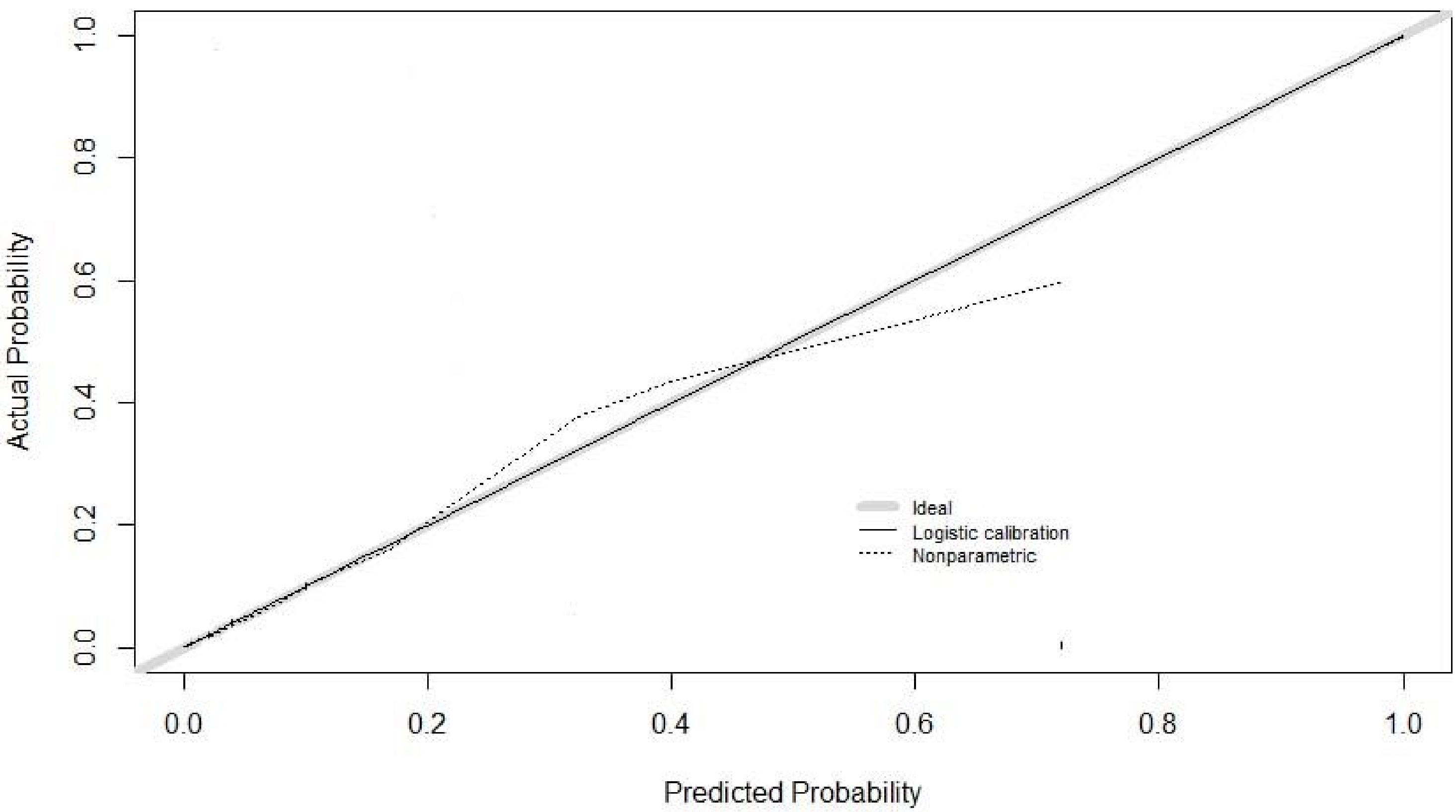

Figure 3

Calibration plot of the nomogram used for predicting intracranial hemorrhage (ICH) atfer thrombolysis

Supplementary Files

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